Review

Canine oral fibrosarcoma: Changes in prognosis over the last 30 years?

Marina Martano *, Selina Iussich, Emanuela Morello, Paolo Buracco

Department of Veterinary Sciences, University of Turin, 10095 Grugliasco, Italy

* Corresponding author. Tel.: +39 11 6709064.
E-mail address: marina.martano@unito.it (M. Martano).

Abstract

Canine oral fibrosarcoma (oFSA) is a malignant, infiltrating, mesenchymal tumour affecting the oral cavity primarily of medium to large middle aged dogs. The diagnosis often is made late in the course of the disease, due to the frequent caudal location of the tumour, and histopathology is not always sufficient to discriminate undifferentiated oFSA from other poorly differentiated malignant mesenchymal tumours occurring at the same site, especially in small biopsy samples. The literature exclusively relating to oFSA is limited and outcome data following treatment are difficult to compare. The purpose of this article is to provide an overview of the literature spanning the last 30 years, specifically with regard to different treatment modalities in their relation to prognosis of canine oFSA.

Overall, the survival rate for dogs with oFSA has improved in recent years (overall survival 247 to 743 days, as opposed to 30 - 540 days in papers published before 2000), probably due to better surgical planning. The major concern in clinical management of canine oFSA is the high local rate of recurrence (up to 57%), whereas metastasis occurs late in about 10-14% of affected dogs. Wide surgical excision is the mainstay of treatment. Initially, the tumour was considered to be radioresistant, but the combination of surgery and radiotherapy seems to be the most promising treatment modality at present. Despite a histopathological diagnosis of a low grade tumour, an aggressive treatment approach is always warranted to cure oFSA, but the ability to control local disease still represents the major challenge.

Keywords: Canine oral fibrosarcoma; En bloc excision; Local recurrence; Prognosis; Radiotherapy

Introduction

Oral tumours represent 6-7% of all canine malignancies and, among these, oral fibrosarcoma (oFSA) accounts for 8-25%, being the third most common malignant neoplasm of the oral cavity in dogs (Liptak and Withrow, 2013). The median age of dogs with oFSA at diagnosis is 8 years, which is slightly younger than dogs diagnosed with malignant melanoma and squamous cell carcinoma of the oral cavity (Liptak and Withrow, 2013). Dogs under 5 years of age at diagnosis are also reported (Todoroff and Brodey, 1979; Hoyt and Withrow, 1984). Medium to large breed dogs (> 20 kg) seem to be more commonly affected. There is no sex predilection, although male dogs are over-represented in some studies (Todoroff and Brodey, 1979; Hoyt and Withrow, 1984). Golden retrievers are over-represented, especially in cases with a variant of the tumour characterised by an aggressive biological behaviour, known as 'high-low' oFSA, despite more benign histological features (Ciekot et al., 1994).

Undifferentiated forms of oFSA may be difficult to distinguish histologically from other poorly differentiated malignant mesenchymal tumours affecting the oral cavity. In these cases, immunohistochemistry (IHC) may be needed to achieve the final diagnosis, even though few specific markers are available (Boy et al., 2005; Smedley et al., 2011; Munday et al., 2017; Ramos-Vara and Borst, 2017).

Most of the literature on oral tumours in dogs encompasses different histotypes and different treatment modalities; therefore, direct comparisons amongst papers are difficult to conduct. There are relatively few articles that focus exclusively on the treatment of canine oFSA and a more than 10 year gap is evident between articles published in the 1990s and recent years (Thrall, 1981; Creasey and Thrall, 1982; Ciekot et al., 1994; Poirier et al., 2006; Frazier et al., 2012; Gardner et al., 2015; Milovancev et al., 2016). The aim of this paper is to review the literature relating to canine oFSA published within the past 30 years, focusing on the changes in treatment, prognosis

and on the improvements made during this time span. Personal experience is also presented briefly (see Appendix: Supplementary Table 1).

Clinical presentation of dogs with oral fibrosarcoma

Oral FSAs in dogs usually appear as firm, pink to red, swellings or masses, frequently involving the gingiva of the maxilla, and the hard and soft palate; the underlying bone can be invaded in up to 72% of cases. As the tumour progresses, ulceration of the mass may occur, as well as facial deformity (Liptak and Withrow, 2013). Clinical signs may be minimal initially and owners may notice the problem only late in the course of the disease, especially for more caudally located tumours. In addition to facial swelling, other clinical signs may be drooling of blood-tinged saliva, when ulceration is present, and, less often, foul odour or difficulty in prehending food.

'High-low' oral fibrosarcoma

The growth rate of oFSA can be variable, depending on the histological grade. Ciekot et al. (1994) first described a unique subtype of FSA known as 'histologically low grade, yet biologically high grade, fibrosarcoma' ('high-low' FSA), which is characterised by a histologically low grade diagnosis despite a high grade clinical behaviour. Twenty-five dogs with 'high-low' oFSA were included in that study, with a range of 3 to 13 years of age (median 8 years). There was an almost even distribution among sexes, but a higher frequency (52%) in Golden retrievers. Sixteen tumours occurred in the maxilla. On histological examination, all specimens were characterised by '*haphazard proliferation of fibrous connective tissue with moderately low to low cellularity, abundant collagenous stroma, minimal nuclear pleomorphism, low mitotic rate, and poor demarcation from surrounding tissue. Invasion of the fibrous tissue into surrounding muscle and bone*' was sometimes evident. Some of the cases had been diagnosed previously as nodular fasciitis. The treatment of these dogs included variable combinations of radical surgery, radiation, chemotherapy and hyperthermia. The initial staging was negative for lung or lymph node

metastasis, except for one dog that already had lymph node involvement; metastases to lung or lymph node subsequently developed in 12-20% of cases, respectively. Since then, this tumour entity has been widely recognised and it is now understood that the treatment should not differ from the standard for dogs with higher grade oFSAs.

Establishing a diagnosis

Clinical staging

As for any malignant tumour, the first step is to establish a clear diagnosis, to evaluate the extent of local tumour infiltration and to screen for local and distant metastases (clinical staging). Staging includes thorough physical examination of the oral cavity and regional lymph nodes, three-view thoracic radiographs, and complete pre-anaesthetic blood and heart evaluation. Since computed tomography (CT) is now widely available, it is usually preferred over radiography to evaluate the extent of infiltration of the primary tumour in the skull; CT also allows evaluation of adjacent bone invasion (Fig. 1 a, b), assists in surgical planning, and thoracic CT is more sensitive than radiographs in detecting lung metastasis (Ghirelli et al., 2013). Moreover, CT allows evaluation of local non-palpable lymph nodes, such as the medial retropharyngeal and parotid lymph nodes. However, a recent study contradicts this statement, showing that this diagnostic tool demonstrates poor sensitivity in the detection of lymph node metastasis from tumours of canine head, particularly for micrometastasis (Skinner et al., 2018). Magnetic resonance imaging (MRI) may also be used for staging purposes, as it is superior in evaluation of soft tissue involvement compared to CT (Vestraete, 2005; Johnson et al., 2016).

Fine needle aspiration of any enlarged lymph node should be performed for clinical staging. However, lymphadenectomy and histology should be considered to reliably determine lymph node status. Fine needle aspiration of the primary mass is often unrewarding, because of the difficulty in collecting a sufficient number of cells for interpretive analysis by cytology, due to the intrinsic

characteristics of mesenchymal tumours, and because of concurrent local inflammation and necrosis. An incisional biopsy of the primary mass is mandatory to achieve diagnosis (Harvey, 1980; Richardson et al., 1983; Hoyt and Withrow, 1984; Vestraete, 2005). However, some authors argue that, since malignant histological type strongly influences survival, but has a minimal impact on the surgical plan, it may be left up to the clinician to propose whether or not to perform an incisional biopsy. This choice is based on the owner's decision whether or not to treat depending on the prognosis, or on cases where there is doubt regarding the malignancy of the lesion or when treatment modalities other than surgery are preferred (Birchard and Carothers, 1990; Berg, 1998; Liptak and Lascelles, 2012).

When performing an incisional biopsy of the primary mass, care should be taken to gain access to the lesion from the oral cavity instead through the skin, to avoid dissemination of the tumour. Accurate site and size of biopsy are also important, since necrosis and inflammation, which usually accompany tumour growth, could lead to false negative results. In some cases, multiple biopsies may be needed, since the diagnosis of oral fibrosarcoma is not always easy to reach and histopathology may not be sufficient. Incisional biopsies should not adversely affect the definitive surgical procedure; therefore, central sampling should be preferred over sampling the periphery of the tumour.

Histopathology

Many articles on histological classification of canine cutaneous and subcutaneous soft tissue sarcomas have been published (Avallone et al., 2007; McSporran 2009; Tamburini et al., 2010; Dennis et al., 2011; Zornhagen et al., 2014; Milovancev et al., 2015). However, few studies have focussed specifically on sarcomas located in the oral cavity, since these are traditionally considered to be a separate entity, characterised by a more local malignant biological behaviour compared to soft tissue sarcomas at other sites (Kuntz et al., 1997; Dennis et al., 2011; Bray, 2016).

Histologically, oFSAs are composed of '*moderately to poorly differentiated large spindle-shaped cells that are arranged in interlacing bundles separated by small amounts of collagenous matrix*' (Munday et al., 2017). Less cellular differentiation and the presence of more frequent mitotic figures and necrosis, together with an infiltrative growth pattern, allow differentiation from fibroma. The distinction from odontogenic tumours is usually straightforward, unless odontogenic epithelium is not present; in this case, the location of the mass away from the dental arcade may help in the diagnosis. Oral osteosarcoma can be diagnosed when osteoid deposition, recognised as homogeneous eosinophilic extracellular material within the neoplasm, is evident (Munday et al., 2017).

Biopsy samples from oFSAs containing overlying and adjacent epithelium may increase the ability to differentiating this entity from oral spindleoid amelanotic melanocytic tumours, since the sensitivity of the specific melanocytic markers used by IHC may be low if intraepithelial nests of neoplastic cells (one of the criteria commonly used to identify melanocytic tumours) cannot be detected. This variant of oral melanoma may be difficult to differentiate from other spindle cell tumours of the oral cavity on the basis of histopathology alone. IHC with a panel of specific anti-melanocytic antibodies, including anti-melanoma antibody (PNL2), melan-A, tyrosinase-related protein (TRP)-1 and TRP-2, was considered of aid in establishing a diagnosis (Smedley et al., 2011; Munday et al., 2017); other monoclonal antibodies such as anti-melanoma gp100 (S-100) and the Human Melanoma Black 45 (HMB45) may complete the panel for melanocytic tumours detection in dogs. IHC should be performed in cases in which histopathology alone is inconclusive, such as in poorly differentiated tumours; for example, positive immunostaining for myocyte markers, such as anti-actin and anti-desmin, may help in differentiating poorly differentiated oFSA from tumours of muscle origin, such as leiomyosarcoma (Boy et al., 2005), rhabdomyosarcoma and myoepithelial or myofibroblastic tumours. Fibrosarcomas usually also exhibit negative immunostaining for cluster of

differentiation (CD) 31, anti-von Willebrand's factor antibody (factor VIII-associated antigen) and CD34, as opposed to tumours of endothelial origin (haemangiosarcomas, lymphangiosarcomas) (Ramos-Vara and Borst, 2017).

Treatment

Since 1980, amongst articles on canine malignant oral tumours, only very few focus on oFSA exclusively or include a high number of cases, except for some in which the number of dogs with oFSA exceeds 20 (Todoroff and Brodey, 1979; Ciekot et al., 1994; Théon et al., 1997; Poirier et al., 2006; Frazier et al., 2012; Gardner et al., 2015; Sarowitz et al., 2017). Moreover, most of these articles include dogs that have received a variety of different treatment modalities, and the diagnostic approach was not uniform, thus making comparisons difficult.

Oral FSA in dogs is characterised by a high rate of recurrence, which can occur in up to 57% of cases (Todoroff and Brodey, 1979; Salisbury et al., 1986; Kosovsky et al., 1991; Schwarz et al., 1991 a, b; Wallace et al., 1992; Lascelles et al., 2003; Frazier et al., 2012; Sarowitz et al., 2017). In contrast, distant metastases are less common, being detected in 0-35% of cases (Todoroff and Brodey, 1979; Salisbury and Lantz, 1988; Wallace et al., 1992; Ciekot et al., 1994; Poirier et al., 2006; Frazier et al., 2012; Sarowitz et al., 2017). Therefore, the major challenge in treatment is achieving local control. En bloc excision plays an important role in accomplishing this goal, but multimodality treatment, primarily combining surgery and radiation therapy, is the mainstay of treatment (Hoyt and Withrow, 1984; Emms, 1987; Kosovsky et al., 1991; White, 1991; Wallace et al., 1992; Ciekot et al., 1994; Burk, 1996; Berg, 1998; Gardner et al., 2015; Sarowitz et al., 2017).

Surgery

Mandibulectomy and maxillectomy have become the routine methods for treating canine oral malignancies, with good clinical and functional outcome (Withrow and Holmberg, 1983; Bradley et

al., 1984; White et al., 1985; Emms and Harvey, 1986; Salisbury et al., 1986; Salisbury and Lantz, 1988; Birchard and Carothers, 1990; Kosovsky et al., 1991; Schwarz et al., 1991 a, b; White, 1991; Wallace et al., 1992; Fox et al., 1997; Lascelles et al., 2003, 2004; Vestraete, 2005; Sarowitz et al., 2017). However, for oral malignancies, including oFSA, there is still debate about how to determine the safest surgical margins to limit local recurrence. CT or MRI evaluation of the primary lesion is helpful in determining such margins, mainly for caudally located tumours. Most authors report that at least 1 cm of macroscopically normal soft tissue or bone surrounding the tumour should be removed (Bradley et al., 1984; Hoyt and Withrow, 1984; Emms and Harvey, 1986; Kosovski et al., 1991; Wallace et al., 1993; Berg, 1998; Frazier et al., 2012); whenever possible, a margin of 2-3 cm is preferable, but this may not be always possible to achieve (Liptak and Lascelles, 2012; Sarowitz et al., 2017).

Information about the completeness of surgical excision is reported in some publications (Schwarz et al., 1991a, b; Ciekot et al., 1994; Forrest et al., 2000; Lascelles et al., 2003, 2004; Frazier et al., 2012; Gardner et al., 2015; Sarowitz et al., 2017). In larger studies, the proportion of dogs in which tumours could be removed with clean margins was never higher than 71% (Schwarz et al., 1991a). Technical limitations in margin evaluation still remain a challenge, despite improvements made in this field over the past few years and the growing awareness of surgeons to correctly prepare the tissue sample for the pathologist (Milovancev et al., 2017). The role of the tumour microenvironment in promoting tumour invasion and metastasis, as well as the concept of tumour heterogeneity, may help to explain the recurrence of ‘completely excised’ neoplasms (Milovancev and Russell, 2017).

Radiotherapy

In earlier studies, oFSA was considered a radioresistant tumour (Todoroff and Brodey, 1979; Harvey, 1980; Thrall, 1981; Richardson et al., 1983; Harvey, 1985; Emms, 1987; Vestraete, 2005).

This was probably due to the limitations that came with orthovoltage radiation machines (Todoroff and Brodey, 1979; Thrall, 1981; Brewer and Turrel, 1982; Creasey and Thrall, 1982). The combination of orthovoltage radiation with the radiosensitiser misonidazole did not seem to improve the outcome and was associated with side effects (Creasey and Thrall, 1982). Hyperthermia has also been used together with orthovoltage radiotherapy (Brewer and Turrel, 1982; Schwarz et al., 1991a, b), but this combination is now rarely used, due to the difficulty in administering heating and the availability of more advanced radiotherapy machines.

With the advent of megavoltage equipment, in fact, both the incidence and severity of side effects, and the overall results of treatment have improved considerably (Hoyt and Withrow, 1984; Burk, 1996; Théon et al., 1997; Berg, 1998; Dhaliwal et al., 1998; Forrest, 2000; Lascelles et al., 2004; Poirier et al., 2006; Frazier et al., 2012; Gardner et al., 2015). Costs remain the major issue of this treatment modality, especially in some European countries. A high dose of radiation, > 50 Gy, is considered necessary to overcome radioresistance (Poirier et al., 2006).

Radiotherapy alone, with a curative or palliative intent, may be useful for the treatment of canine oFSA, producing similar results to those of surgery alone. In a study conducted by Poirier et al. (2006) on macroscopic oral lesions, the overall times to progression and overall survival were 205 and 310 days, respectively; this is not substantially different from what has been achieved through surgery alone (Lascelles et al., 2004; Sarowitz et al., 2017). Similar results were reported by Gardner et al. (2015) in a smaller group of dogs.

In general, when a curative intent radiation protocol is attempted, a total dose of 40-60 Gy is administered in daily fractions of 3-4.2 Gy, on a Monday through Friday schedule, both in a macroscopic (Poirier et al., 2006) or adjuvant setting (Forrest et al., 2000; Gardner et al., 2015). For palliative purposes, coarsely fractionated protocols, consisting of the administration of a total dose

of 24-30 Gy, delivered in three fractions of 8 Gy each or five fractions of 6 Gy each, have been proposed (Poirier et al., 2006). Nonetheless, oral FSA seems to be less sensitive to radiation when compared to the same histotype growing at other sites (Forrest et al., 2000).

Within the past 15 years, the use of CT scanning for both the early detection of lung metastasis and for surgical planning has almost completely replaced the need for radiographs. Despite this, the recurrence rate still is as high as 54% (Sarowitz et al., 2017) to 57% (Lascelles et al., 2003) when surgery is the sole treatment modality. In the authors' experience of a small case series of 13 oFSAs treated by surgery alone, the recurrence rate was 30.7%, and clean surgical margins could be obtained in 10/13 (76.9%) cases, most of which had CT performed as part of the surgical planning. The median disease-free interval was 317 days and median overall survival was not reached (see Appendix: Supplementary Table 1). A recently published article using the same treatment modality in eight dogs reported a median survival of 249 days and a median progression-free survival of 138 days (Gardner et al. 2015). The combination of surgery and adjuvant megavoltage radiotherapy leads to an improvement of tumour control (recurrence rate 24.1%) and median overall survival (743 days), as reported by Frazier et al. (2012).

Chemotherapy and targeted therapy

Although chemotherapy has been used as adjuvant treatment for oFSA (Emms et al., 1986; Schwarz et al., 1991 a, b; Ciekot et al., 1994; Gardner et al., 2015), its role is still unclear and has not been investigated in detail. As for most sarcomas, oFSA is considered to be chemoresistant (Harvey, 1985). However, the most commonly administered drug in association with surgery and/or radiation is doxorubicin. Recently, the effect of two tyrosine kinase inhibitors (TKI), imatinib and masitinib, on canine oFSA cells and tissue samples was investigated, based on the premise that some canine oFSA samples and two canine oFSA cell lines expressed platelet-derived growth factor receptors (PDGFRs)-α and β (Milovancev et al., 2016). A mild inhibitory effect of both TKIs was

observed in vitro, but at a concentration too high to be used in a clinical setting. The addition of doxorubicin in the cell culture slightly potentiated the action of the TKIs. This finding is worth further investigation in order to use these drugs as adjuvant cytotoxic drugs. A recent publication on dogs affected by malignant tumours showed that the combination of doxorubicin (at a slightly reduced dose) and toceranib appears to be safe (Pellin et al., 2017). Oral FSAs were not included in the study, but it might be worth investigating such a combination in this type of tumour.

In two studies, vascular endothelial growth factor (VEGF) plasma concentrations were measured in dogs with various malignant and benign tumours, including oFSA (Wergin and Kaser-Hotz, 2004; Sobczynska-Rak et al., 2014). In both studies, VEGF concentrations were lower in FSA compared to other malignant tumours, such as oral melanoma and squamous cell carcinoma; however, in the study of Wergin and Kaser-Hotz (2004) the location of the fibrosarcoma was not stated and it is not clear whether oFSA was included.

There are no published data on the use of metronomic chemotherapy for palliative treatment of canine oFSA. This approach is based on the '*oral administration of chemotherapy at relatively low, minimally toxic doses, on a frequent or continuous schedule of treatment, with no extended drug-free breaks*' (Gaspar et al., 2018). The more commonly used drugs are different combinations of cyclophosphamide, chlorambucil and lomustine, together with thalidomide, metformin, piroxicam or other anti-cyclooxygenases (COX) agents, in order to stimulate the host immune system, modify tumour microenvironment and act against tumour neoangiogenesis.

The promising results obtained in dogs affected by soft tissue sarcomas at sites other than the oral cavity may encourage the use of metronomic chemotherapy for oFSA (Emslie et al., 2008; Burton et al., 2011). In particular, the disease-free interval of dogs with incompletely resected soft tissue sarcomas of the trunk and extremities was significantly longer when metronomic chemotherapy was administered (Emslie et al., 2008).

The effects of electrochemogene therapy with a combination of bleomycin and interleukin (IL)-12 on different histotypes of spontaneous canine tumours were reported by Reed et al. (2010). This technique is based on the ability to increase cell permeability and allow movement of molecules into cells by the application of a series of square-wave electrical pulses (electroporation) to the tumour mass. This may be applied to both gene and drug therapy. In the study conducted by Reed et al. (2010) one inoperable oFSA was included, and an initial partial response was seen before progressive disease developed. The authors concluded that this tumour type might be partially responsive to this treatment, with mild side effects; therefore, this technique may be worthy of further investigation, mainly for non-resectable cases.

Prognosis

Local tumour control still represents the main challenge in canine oFSA. Literature beyond the year 2000 was chosen for evaluating prognosis of oFSA. Most of the articles published after that time included CT scanning as part of clinical staging, compared to previous reports where thoracic and skull radiographs were performed most frequently for clinical staging purposes. Including more advanced imaging modalities should have improved the ability to better plan the surgical excision. Nonetheless, the incidence of local recurrence has not improved as much as expected.

One year survival

The one year survival, regardless of the type of treatment, is reported as 7-76% in studies published before 2000 (Todoroff and Brodey, 1979; Harvey, 1980; Thrall, 1981; Brewer and Turrel, 1982; White, 1985; Emms and Harvey, 1986; Kosovsky et al., 1991; White, 1991; Wallace et al., 1992; Théon et al., 1997) compared to 29.4-87.7% for studies published from 2000 to 2017 (Poirier et al., 2006; Frazier et al., 2012; Sarowitz et al., 2017; personal data, see Appendix: Supplementary Table 1). However, when analysing the data by Mann-Whitney *U* test (Prism v5.0, GraphPad

Software), a statistically significant difference was not evident between these two periods ($P = 0.23$; Fig. 2).

Overall survival time

In contrast, when comparing overall survival time, a statistically significant improvement ($P = 0.035$) was found among groups. The overall survival reported before the 2000 was 30-540 days (Todoroff and Brodey, 1979; Harvey, 1980; Thrall, 1981; Brewer and Turrel, 1982; Bradley et al., 1984; Emms et al., 1986; Salisbury et al., 1986; Salisbury and Lantz, 1988; Kosovsky et al., 1991; Schwarz et al.,1991 a, b; Wallace et al., 1992; Fox et al., 1997) compared to 247-743 days reported in later studies (Forrest et al., 2000; Poirier et al., 2006; Ohlerth et al., 2010; Frazier et al., 2012; Gardner et al., 2015; Sarowitz et al., 2017) (Fig. 3). The difference between the one-year and overall survival could be explained in part by the low number of cases in many of the papers considered, that may have influenced this result. The biology of the tumour, that can be sometimes slow-growing, could also influence the time to progression (both in terms of time to recurrence or metastasis), since it may be longer than one year, thus resulting in a statistically different survival only on the long run. A prospective study enrolling an adequate number of cases followed for at least 2 years would be warranted to clarify this issue.

Metastasis

The metastatic rate has not changed substantially throughout the years ($P = 0.40$); a range of 0-38.4% is reported in earlier publications (Todoroff and Brodey, 1979; Bradley et al., 1984; White et al., 1985; Emms and Harvey, 1986; Salisbury et al., 1986; Salisbury and Lantz, 1988; Kosovsky et al., 1991; Schwarz et al.,1991 a, b; White, 1991; Wallace et al., 1992; Ciekot et al., 1994; Théon et al., 1997), compared to 0-23% more recently (Lascelles et al., 2003, 2004; Poirier et al., 2006; Frazier et al., 2012; Sarowitz et al., 2017; personal data, see Appendix: Supplementary Table 1) (Fig. 4).

Recurrence

The recurrence rate was 5-87.5% in earlier publications (Todoroff and Brodey, 1979; Harvey et al., 1980; Thrall, 1981; Brewer and Turrel, 1982; Creasey and Thrall, 1982; Withrow and Holmberg, 1983; Bradley et al., 1984; White et al., 1985; Emms and Harvey, 1986; Salisbury et al., 1986; Salisbury and Lantz, 1988; Kosovsky et al., 1991; Schwarz et al.,1991a, b; White, 1991; Wallace et al., 1992; Ciekot et al., 1994; Théon et al., 1997), compared to 24.1-57.1% in more recent reports (Lascelles et al., 2003, 2004; Frazier et al., 2012; Sarowitz et al., 2017; personal data in Supplementary files); these ranges are not significantly different ($P = 0.68$; Fig. 5).

Time to recurrence

Similarly, the time to recurrence has not changed significantly between the two evaluated time periods ($P = 0.26$); before 2000, tumours recurred after 75-1260 days (Todoroff and Brodey, 1979; Harvey, 1980; Thrall, 1981; Brewer and Turrel, 1982; White, 1985; Emms and Harvey, 1986; Kosovsky et al., 1991; White, 1991; Wallace et al., 1992; Théon et al., 1997), whereas the time to recurrence was 145-1368 days in the more recent literature (Forrest et al., 2000; Lascelles et al., 2004; Poirier et al., 2006; Frazier et al., 2012; Gardner et al., 2015; Sarowitz et al., 2017; personal data, see Appendix: Supplementary Table 1).

Prognostic factors

A few authors have evaluated prognostic factors for long-term survival and disease-free interval. Tumour stage, tumour site (more caudally located masses have a worse prognosis), and completeness of surgical excision were reported most frequently (Salisbury and Lantz, 1988; Schwarz et al., 1991 a, b; Wallace et al., 1992; Théon et al., 1997; Gardner et al., 2015; Sarowitz et al., 2017).

Conclusions

Oral FSA is a malignant, infiltrating mesenchymal tumour affecting the oral cavity of middle-aged dogs. The diagnosis is often made late in the course of the disease because of the frequent caudal location of the tumour. Distant metastases are rarely evident at presentation. Although histopathology may be compatible with a low-grade tumour, an aggressive approach is always warranted to obtain local control of this invasive tumour. Within the last 30 years, some improvements have been made in equipment for radiotherapy and in the surgical procedures available, but the prognosis for this tumour is still guarded. Treatment failure is often due to local tumour recurrence that can still occur in up to 54% of cases. A thorough staging based on CT examination and wide/radical surgical excision is fundamental to eradicate the tumour. Adjuvant treatments, such as radiation therapy, are recommended in order to prolong both the disease-free interval and survival time. A rigorous analysis of the published literature is challenging due to small case series and the many different treatment modalities that were included even in the same study; therefore, the data presented here should be considered cautiously. Nevertheless, an improvement in survival has occurred in recent years, and an optimistic view on the possibility to cure this tumour is justified. Prospective studies focusing on oral FSA and investigating the roles of cytotoxic and targeted chemotherapy, as well as radiotherapy, would be needed to clearly address the best treatment options for this tumour in dogs.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

Acknowledgements

The authors wish to express gratitude to Dr Paola Pregel for support in the statistical analysis.

Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:

…

References

Avallone, G., Helmbold, P., Caniatti, M., Stefanello, D., Nayak, R.C., Roccabianca P., 2007. The spectrum of canine cutaneous perivascular wall tumors: Morphologic, phenotypic and clinical characterization. Veterinary Pathology 44, 607-620.

Berg, J., 1998. Principles of oncologic orofacial surgery. Clinical Techniques in Small Animal Practice 13, 38-41.

Birchard, S., Carothers, M., 1990. Aggressive surgery in the management of oral neoplasia. Veterinary Clinics of North America: Small Animal Practice 20, 1117-1140.

Boy, S.C., Van Heerden, W.F.P., Steenkamp, G., 2005. Diagnosis and treatment of primary intraoral leiomyosarcomas in four dogs. Veterinary Record 156, 510-513.

Bradley, R.L., MacEwen, E.G., Loar, A.S., 1984. Mandibular resection for removal of oral tumors in 30 dogs and 6 cats. Journal of the American Veterinary Medical Association 184, 460-463.

Bray, J.P., 2016. Soft tissue sarcoma in the dog - part 1: A current review. Journal of Small Animal Practice 57, 510-519.

Brewer, W.G. Jr, Turrel, J.M., 1982. Radiotherapy and hyperthermia in the treatment of fibrosarcoma in the dog. Journal of the American Veterinary Association 181, 146-150.

Burk, R.L., 1996. Radiation therapy in the treatment of oral neoplasia. Veterinary Clinics of North America: Small Animal Practice 26, 155-163.

Burton, J.H., Mitchell, L., Thamm, D.H., Dow, S.W., Biller, B.J., 2011. Low-dose cyclophosphamide selectively decreases regulatory T cells and inhibits angiogenesis in dogs with soft tissue sarcoma. Journal of Veterinary Internal Medicine 25, 920-926.

Ciekot, P.A., Powers, B.E., Withrow, S.J., Straw, R.C., Ogilvie, G.K., LaRue, S.M., 1994. Histologically low-grade, yet biologically high-grade, fibrosarcomas of the mandible and maxilla in dogs: 25 cases (1982-1991). Journal of the American Veterinary Medical Association 204, 610-615.

Creasey, W.A., Thrall, D.E., 1982. Pharmacokinetic and anti-tumor studies with the radiosensitizer misonidazole in dogs with spontaneous fibrosarcomas. American Journal of Veterinary Research 43, 1015-1018.

Dennis, M.M., McSporran, K.D., Bacon, N.J., Schulman, F.Y., Foster, R.A., Powers, B.E., 2011. Prognostic factors for cutaneous and subcutaneous soft tissue sarcomas in dogs. Veterinary Pathology 48, 73-84.

Dhaliwal, R.S., Kitchell, B.E., Manfra Marretta, S., 1998. Oral tumors in dogs and cats. Part II. Prognosis and treatment. Compendium on Continuing Education 20, 1109-1119.

Elmslie, R.E., Glawe, P., Dow, S.W., 2008. Metronomic therapy with cyclophosphamide and piroxicam affectively delays tumor recurrence in dogs with incompletely resected soft tissue sarcomas. Journal of Veterinary Internal Medicine 22, 1373-1379.

Emms, S.G., Harvey, C.E., 1986. Preliminary results of maxillectomy in the dog and cat. Journal of Small Animal Practice 27, 291-306.

Emms, S.G., 1987. The management of oral tumours in dogs and cats. Australian Veterinary Journal 64, 22-25.

Forrest, L.J., Chun, R., Adams, W.M., Cooley, J., Vail, D.M., 2000. Postoperative radiotherapy for canine soft tissue sarcoma. Journal of Veterinary Internal Medicine 14, 578-582.

Fox, L.E., Geoghegan, S.L., Davis, L.H., Hartzel, J.S., Kubilis, P., Gruber, L.A., 1997. Owner satisfaction with partial mandibulectomy or maxillectomy for treatment of oral tumors in 27 dogs. Journal of the American Animal Hospital Association 33, 25-31.

Frazier, S.A., Johns, S.M., Ortega, J., Zwingenberger, A.L., Kent, M.S., Hammond, G.M., Rodriguez, C.O. Jr, Steffey, M.A., Skorupski, K.A., 2012. Outcome in dogs with surgically resected oral fibrosarcoma (1997-2008). Veterinary and Comparative Oncology 10, 33-43.

Gardner, H., Fidel, J., Haldorson, G., Dernell, W., Wheeler, B., 2015. Canine oral fibrosarcomas: A retrospective analysis of 65 cases (1998-2010). Veterinary and Comparative Oncology 13, 40-47.

Gaspar, T.B., Henriques, J., Marconato, L., Queiroga, F. L., 2018. The use of low-dose metronomic chemotherapy in dogs - insight into a modern cancer field. Veterinary and Comparative Oncology 1, 2-11.

Ghirelli, C.O., Villamizar, L.A., Pinto, A.C., 2013. Comparison of standard radiography and computed tomography in 21 dogs with maxillary masses. Journal of Veterinary Dentistry 30, 72-76.

Harvey, H.J., 1980. Cryosurgery of oral tumors in dogs and cats. Veterinary Clinics of North America: Small Animal Practice 10, 821-830.

Harvey, H.J., 1985. Oral tumors. Veterinary Clinics of North America: Small Animal Practice 15, 493-500.

Hoyt, M.F., Withrow, S.J., 1984. Oral malignancy in the dog. Journal of the American Animal Hospital Association 20, 83-92.

Johnson, P.J., Elders, R., Pey, P., Dennis, R., 2016. Clinical and magnetic resonance imaging features of inflammatory versus neoplastic medial retropharyngeal lymph node mass lesions in dogs and cats. Veterinary Radiology and Ultrasound 17, 24-32.

497 Kosovsky, J.K., Matthiesen, D.T., Marretta, S.M., Patnaik, A.K., 1991. Results of partial
498 mandibulectomy for the treatment of oral tumors in 142 dogs. Veterinary Surgery 20, 397-
499 401.
500
501 Kuntz, C.A., Dernell, W.S., Powers, B.E., Devitt, C., Straw, R.C., Withrow, S.J., 1997. Prognostic
502 factors for surgical treatment of soft tissue sarcomas in dogs: 75 cases (1986-1996). Journal of
503 the American Veterinary Medical Association 211, 1147-1151.
504
505 Lascelles, B.D., Thomson, M.J., Dernell, W.S., Straw, R.C., Lafferty, M., Withrow, S.J., 2003.
506 Combined dorsolateral and intraoral approach for the resection of tumors of the maxilla in the
507 dog. Journal of the American Veterinary Medical Association 39, 294-305.
508
509 Lascelles, B.D., Henderson, R.A., Seguin, B., Liptak, J.M., Withrow, S.J., 2004. Bilateral rostral
510 maxillectomy and nasal planectomy for large rostral maxillofacial neoplasms in six dogs and
511 one cat. Journal of the American Veterinary Medical Association 40, 137-146.
512
513 Liptak, J.M., Lascelles, D.X., 2012. Oral tumors. In: Kudnig, S.T., Séguin, B. (Eds) Veterinary
514 Surgical Oncology, 1st Edn. Wiley-Blackwell, West Sussex, UK, pp. 119-178.
515
516 Liptak, J.M., Withrow, S.J., 2013. Cancer of the gastrointestinal tract. In: Withrow, S.J., Vail, D.M.,
517 Page, R.L. (Eds) Small Animal Clinical Oncology, 5th Edn. Elsevier, St Louis, Missouri,
518 USA, pp. 318-398.
519
520 McSporran, K.D., 2009. Histologic grade predicts recurrence for marginally excised canine
521 subcutaneous soft tissue sarcomas. Veterinary Pathology 46, 928-933.
522
523 Milovancev, M., Hauck, M., Keller, C., Stranahan, L.W., Mansoor, A., Malarkey, D.E., 2015.
524 Comparative pathology of canine soft tissue sarcomas: Possible models of human non-
525 rhabdomyosarcoma soft tissue sarcomas. Journal of Comparative Pathology 152, 22-27.
526
527 Milovancev, M., Helfand, S.C., Marley, K., Goodall, C.P., Löhr, C.V., Bracha, S., 2016.
528 Antiproliferative effects of masitinib and imatinib against canine oral fibrosarcoma in vitro.
529 BMC Veterinary Research 12, 85.
530
531 Milovancev, M., Russel, D.S., 2017. Surgical margins in the veterinary cancer patient. Veterinary
532 and Comparative Oncology 15, 1136-1157.
533
534 Milovancev, M.M., Townsend, K.L., Gorman, E., Bracha, S., Curran, K., Russell, D.S., 2017.
535 Shaved margin histopathology and imprint cytology for assessment of excision in canine mast
536 cell tumors and soft tissue sarcomas. Veterinary Surgery 46, 879-885.
537
538 Munday, J.S., Löhr, C.V., Kiupel, M., 2017. Tumors of the Alimentary Tract. In: Meuten, D.J. (Ed.)
539 Tumors in Domestic Animals, 5th Edn. John Wiley & Sons, New York, USA, pp. 509-511.
540
541 Ohlerth, S., Bley, C.R., Laluhová, D., Roos, M., Kaser-Hotz, B., 2010. Assessment of changes in
542 vascularity and blood volume in canine sarcomas and squamous cell carcinomas during
543 fractionated radiation therapy using quantified contrast-enhanced power Doppler
544 ultrasonography: A preliminary study. The Veterinary Journal 186, 58-63.
545
546 Pellin, M.A., Wouda, R.M., Robinson, K., Tsimbas, K., Kurzman, I.D., Biller, B.J., Vail, D.M.,
547 2017. Safety evaluation of combination doxorubicin and toceranib phosphate (Palladia®) in

tumour bearing dogs: A phase I study-finding study. Veterinary and Comparative Oncology 3, 919-931.

Poirier, V.J., Rohrer Bley, C., Roos, M., Kaser-Hotz, B., 2006. Efficacy of radiation therapy for the treatment of macroscopic canine oral soft tissue sarcoma. In vivo 20, 415-420.

Ramos-Vara, J.A., Borst, L.B., 2017. Immunohistochemistry: Fundamentals and applications in oncology. In: Meuten, D.J. (Ed.) Tumors in Domestic Animals, 5th Edn. John Wiley & Sons, New York, USA, pp. 374-392.

Reed, S.D., Fulmer, A., Buchholz, J., Zhang, B., Cutrera, J., Shiomitsu, K., Li, S., 2010. Bleomycin/interleukin-12 electrochemogene therapy for treating naturally occurring spontaneous neoplasms in dogs. Cancer Gene Therapy 17, 571-578.

Richardson, R.C., Jones, M.A., Elliott, G.S., 1983. Oral neoplasms in the dog: A diagnostic and therapeutic dilemma. Compendium on Continuing Education 5, 441-446.

Salisbury, S.K., Richardson, D.C., Lantz, G.C., 1986. Partial maxillectomy and premaxillectomy in the treatment of oral neoplasia in the dog and cat. Veterinary Surgery 15, 16-26.

Salisbury, S.K., Lantz, G.C., 1988. Long-term results of partial mandibulectomy for treatment of oral tumors in 30 dogs. Journal of the American Animal Hospital Association 24, 285-294.

Sarowitz, B.N., Davis, G.J., Kim, S., 2017. Outcome and prognostic factors following curative-intent surgery for oral tumours in dogs: 234 cases (2004 to 2014). Journal of Small Animal Practice 58, 146-153.

Schwarz, P.D., Withrow, S.J., Curtis, C.R., Powers, B.E., Straw, R.C., 1991. Mandibular resection as a treatment for oral cancer in 61 dogs. Journal of the American Animal Hospital Association 27, 601-610.

Schwarz, P.D., Withrow, S.J., Curtis, C.R., Powers, B.E., Straw, R.C., 1991. Partial maxillary resection as a treatment for oral cancer in 81 dogs. Journal of the American Animal Hospital Association 27, 617-624.

Skinner, O.T., Boston, S.E., Giglio, R.F., Whitley, E.M. Colee, J.C., Porter, E,G., 2018. Diagnostic accuracy of contrast-enhanced computed tomography for assessment of mandibular and medial retropharyngeal lymph node metastasis in dogs with oral and nasal cancer. Veterinary and Comparative Oncology. July 10, Epub ahead of print.

Smedley, R.C., Lamoureux, J., Sledge, D.G., Kiupel, M., 2011. Immunohistochemical diagnosis of canine oral amelanotic melanocytic neoplasms. Veterinary Pathology, 48, 32-40.

Sobczynska-Rak, A., Polkowska, I., Silmanowicz, P., 2014. Elevated vascular endothelial growth factors (VEGF) levels in the blood serum of dogs with malignant neoplasms of the oral cavity. Acta Veterinaria Hungarica 62, 362-371.

Tamburini, B.A., Phang, T.L., Fosmire, S.P., Scott, M.C., Trapp, S.C., Duckett, M.M., Robinson, S.R., Slansky, J.E., Sharkey, L.C., Cutter, G.R., et al., 2010. Gene expression profiling identifies inflammation and angiogenesis as distinguishing features of canine hemangiosarcoma. BMC Cancer 10, 619.

599
600 Théon, A.P., Rodriguez, C., Madewell, B.R., 1997. Analysis of prognostic factors and patterns of
601 failure in dogs with malignant oral tumors treated with megavoltage irradiation**.** Journal of the
602 American Veterinary Medical Association 210, 778-784.
603
604 Thrall, D.E., 1981. Orthovoltage radiotherapy of oral fibrosarcomas in dogs. Journal of the
605 American Veterinary Medicine Association 179, 159-162.
606
607 Todoroff, R.J., Brodey, R.S., 1979. Oral and pharyngeal neoplasia in the dog: A retrospective
608 survey of 361 cases. Journal of the American Veterinary Medical Association 175, 567-571.
609
610 Vestraete, F.J.M., 2005. Mandibulectomy and maxillectomy. Veterinary Clinics of North America:
611 Small Animal Practice 35, 1009-1039.
612
613 Wallace, J., Matthiesen, D.T., Patnaik, A.K., 1992. Hemimaxillectomy for the treatment of oral
614 tumors in 69 dogs. Veterinary Surgery 21, 337-341.
615
616 Wergin, M.C., Kaser-Hotz, B., 2004. Plasma vascular endothelial growth factor (VEGF) measured
617 in seventy dogs with spontaneously occurring tumours. In Vivo. 18, 15-20.
618
619 White, R.A.S., Gorman, N.T., Watkins, S.B., Brearley, M.J., 1985. The surgical management of
620 bone-involved oral tumours in the dog. Journal of Small Animal Practice 26, 693-708.
621
622 White, R.A.S., 1991. Mandibulectomy and maxillectomy in the dog: Long term survival in 100
623 cases. Journal of Small Animal Practice 32, 69-74.
624
625 Withrow, S.J., Holmberg, D.L., 1983. Mandibulectomy in the treatment of oral cancer. Journal of
626 the American Animal Hospital Association 19, 273-286.
627
628 Zornhagen, K.W., Kristensen, A.T., Hansen, A.E., Oxboel, J., Kjær, A., 2014. Selection of suitable
629 reference genes for normalization of genes of interest in canine soft tissue sarcomas using
630 quantitative real-time polymerase chain reaction. Veterinary and Comparative Oncology 13,
631 485-493.
632

633 **Figure legends**

634

635 Fig. 1. Computed tomography (CT) images of an oral mass diagnosed as fibrosarcoma. (a) Post
636 contrast scan showing bone involvement of the maxilla and invasion into the nasal cavity. (b) Soft
637 tissue involvement in the same dog. In this case, surgery was not performed since the owners
638 refused neoadjuvant radiation following surgical debulking.

639

640 Fig. 2. One year survival rate reported by different authors before (7-76%) and after (29.4 - 87.7%)
641 the year 2000. Various combinations of surgery, radiotherapy, hyperthermia, chemotherapy were
642 used in different studies. The difference between the two groups is not statistically different (P =
643 0.23).

644

645 Fig. 3. Overall survival reported by different authors before (30-6204 days) and after (247-743
646 days) the year 2000. Different combinations of treatment were used. A significant improvement in
647 survival in recent years was evident (P = 0.035).

648

649 Fig. 4. Metastatic rate reported by different authors before (0-38%) and after (0-23%) the year 2000.
650 There was no significant difference between time periods (P = 0.40).

651

652 Fig. 5. Median recurrence rate reported before (5-87.5%) and after (24.1-57.1%) the year 2000. A
653 significant improvement in tumour control has not been achieved (P = 0.68).

654

655 Fig. 6. Median time to recurrence before (75-1260 days) and after (145- 1368 days) the year 2000.
656 There was no significant difference between time periods (P = 0.26).